Pulmonary Hyaline Membrane Disease

A Panel Discussion

Pathogenesis

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THERE IS A GREAT DEAL of data available on the pathogenesis of hyaline membrane disease—some of it conflicting. Originally it was thought that the eosinophilic membrane could be aspirated amniotic fluid. But hyaline material cannot be demonstrated in amniotic fluid. In addition, if amniotic fluid is put into the tracheal tree of animals—even very young animals—very few develop pulmonary hyaline membranes. However, if amniotic fluid is put into the trachea of young animals and then they are exposed to high oxygen concentration, hyaline membrane develops in the lungs of a very high proportion. It should be noted, though, that in the experiments in which this observation was made, the oxygen concentrations were much greater than used to be used for babies before oxygen was inculpated as a factor in retrolental fibroplasia. Nevertheless, we have to consider the possibility that the combination of aspirated amniotic fluid and a high oxygen concentration may be a factor. Dr. Edith Potter[8] some months ago told me that there appeared to be a definite decrease in the incidence of hyaline membrane disease. At that time, she thought possibly it was related to the fact that they were using much less oxygen; but later, in a letter to Dr. Cantor, she said she was unwilling to intimate with any certainty that decreased use of oxygen might be relevant. Other observers have observed no decrease in incidence in spite of reduced use of oxygen.

Well, if hyaline doesn't come from aspiration, then perhaps it is from exudate. Most of the hyaline material is not really in the alveoli. Most of it is in the terminal bronchioles. It tends to obstruct the terminal bronchioles and then we see areas of atelectasis—sometimes of emphysema, but mostly of atelectasis perhaps secondary to the obstructing hyaline membrane material. Perhaps it is not a complete exudate but simply plasma. If so, then perhaps it is fibrin. Fibrin, when stained in the same way, is eosinophilic and could look just like hyaline membrane. Gitlin[5] and associates have good evidence that a large portion of the material is indeed fibrin. On the other hand, a high proportion is mucoprotein, much higher than the proportion of mucoprotein in plasma. The Canadians have some good evidence suggesting that the material isn't just plasma but rather a concentrated exudate passed through the capillaries of the bronchial wall. It could be a combination of things. For example, perhaps amniotic fluid acts like a thromboplastic material on exudation of plasma and causes coagulation and clotting of the plasma more rapidly. Perhaps that combination is responsible for the rapid formation of hyaline membrane. This idea would fit certain other things we know about this entity. For example, hyaline membranes are not present in stillborns. They occur only in infants that have taken a first breath. Hence, it is conceivable that something happens after the baby is born and takes a first breath—that there is then plasma exuding through the capillary walls into the lungs, that there is amniotic fluid with thromboplastic activity causing coagulation of the protein, and fibrin is deposited. Where the mucoprotein comes from in such high concentrations we don't know.

Lieberman[6] (a member of the panel) has done some fascinating work in this field. His point was this: Perhaps it is not too abnormal for fibrin to appear in the lungs. Perhaps it is gotten rid of by an enzyme system which involves plasminogen. This supposes a plasminogen precursor or activator and that the plasminogen has lytic action on whatever fibrin forms. Trouble occurs if lysis does not take place, perhaps because of absence of or relative absence of plasminogen or its precursor in the lung. Lieberman conjectures this deficiency may be genetically related. (We do know that there are mothers who have not just one baby with hyaline membrane disease but two or three.) He therefore suggests that there is an absence of the enzyme system which would normally reduce fibrin and get rid

Submitted September 28, 1959.

of it as rapidly as it forms, and that the absence may be genetically determined.

Certain things are bothersome about this idea which I hope Dr. Lieberman will comment upon. It can't be a dominant genetic factor, because mothers who have babies with this disease often have subsequent babies who don't have it. In addition to that, I understand that Craig[2] in Boston exposed hyaline membranes to plasminogen-like substance and found that it took a very high concentration over three hours to reduce the fibrin. It would seem that in babies there could not be enough plasminogen present long enough to bring about lysis of hyaline membranes. Of course, its presence early might have a preventive effect. Perhaps there is an inactivator present in concentration sufficient to inactivate the enzyme or its precursor and thus permit the formation of hyaline membrane.

It is possible that none of these conjectures apply. The hyaline membrane formation could be a terminal phenomenon. We know that hyaline membranes are formed in adults, for example, who have had influenza, sometimes in rheumatic fever, in radiation pneumonia and in various poisonings such as war gas poisoning. So, perhaps the membrane is, as some observers like to call it, an eosinophilic herring—not the main problem.

Some quite fascinating reports were given at a recent meeting of the American Pediatric Society and the Society for Pediatric Research. There were four individual reports from Clement Smith's group[1,3,4,7] in Boston. They catheterized the hearts of infants with clinical hyaline membrane disease and were able to demonstrate a functional ductus, a very patent ductus with a good flow of blood from one side to the other. They could not demonstrate these ducti clinically. In addition, they found that the pressure in the pulmonary arterial system, as well as on the systemic side of the heart, was low, but the pulmonary vein pressure was high. Now if you think about that for a minute, it suggests that the baby might be in cardiac failure—output failure on both sides, left and right. But they digitalized such infants and observed no benefit from the digitalization. That still doesn't rule out the possibility that there is some cardiac failure. At any rate, facts from these data establish that the arterial pressures are low. Now if the venous pressure is high, this again would fit with the possibility of transudation or exudation from the capillaries into the lung itself.

In addition to this, they found that blood pressure in the arm drops transiently but decidedly about a half hour after birth in infants who develop respiratory distress.

In a very interesting study reported from Rochester,[9] New York, it was noted that there was a pronounced increase in blood volume in normal babies, as much as 20 per cent, within three to five hours after birth—not just in the plasma portion but in the red cell mass as well. Where this extra blood comes from is in some doubt, but it would appear to come probably from the lungs. The lungs are fairly solid in utero and perhaps contain a lot of blood. After they are aerated some of that blood is squeezed out in the first 3 to 5 hours, which would act like a transfusion, the infant suddenly having 50 or 60 cc. more of circulating whole blood. Now keep this report from Rochester in mind in considering one from Pittsburgh[10] which was also presented. In the latter, it was found that in full-term babies there were more respiratory difficulties when the cord was clamped early than when it was clamped late. With premature babies the converse was true. It was thought that the reason might be that late clamping in premature babies gave the baby an additional 50 to 60 cc. of blood from the placenta and cord. If this were in addition to the 50 or 60 cc. from the lung that the Rochester group noted, the effect would be quite an increase in blood volume. Infants born by cesarean section are known to have an excess of body water and more hyaline membrane disease. To conjecture further, supposing a large increase in blood volume, a large ductus and a drop in both systemic and pulmonary arterial pressure, the infant might get quite a pooling of blood in the lungs, which might make for exudation or transudation of plasma into the alveoli and lead to the formation of a hyaline membrane.

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